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The value of early hemodynamic parameters in neonates with septic shock

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ABSTRACT: This study aims at determining the value, if any, of hemodynamic parameters in early septic shock incidence among the neonatal population. Eighty-two neonates with septic shock were divided into “survivors” and “non-survivors” according to their survival status within 4 weeks (28-days). The differences in stroke volume (SV), cardiac output (CO), cardiac index (CI) and systemic vascular resistance index (SVRI) were compared between survivors and non-survivors. Receiver operating characteristic (ROC) curves for 28-day mortality were constructed to compare the area under the curve (AUC) among SV, CO and CI. The test characteristics of the different cut-off values, including sensitivity, specificity, area under the ROC curve (AUC), positive likelihood and negative likelihood ratio were equally examined. Of 82 cases of neonates with septic shock in this study, 52 were survivors and 30 non-survivors. The hemodynamic parameters of SV, CO and CI were higher in survivors than in non-survivors (all $p < 0.05$). The AUC values of SV, CO and CI to predict 28-day mortality were 0.724, 0.742, and 0.729, respectively. Stroke volume had sensitivity, specificity, PPV, and NPV of 75.0, 75.0, 40.9 and 92.9%, respectively. Cardiac output had sensitivity, specificity, PPV, and NPV of 91.7, 55.7, 67.6 and 96.7%, respectively. CI had sensitivity, specificity, PPV, and NPV of 91.7, 67.3, 60.7 and 97.2%, respectively. CO achieved the highest AUC, sensitivity and PPV. In conclusion, SV, CO and CI may be valuable in the early stage of septic shock among the neonates.

Keywords: Hemodynamics, neonates, ROC curve, septic shock, value.

INTRODUCTION

With regards to shock cases, children admitted to intensive care units often present septic shock as the most common type of shock. It has been identified as the leading cause of morbidity and mortality among the neonatal population, especially in sub-Saharan Africa (sSA). Septic shock is a common cause of death in critical neonates. The incidence of septic shock was 1.3 to 5.6% in Neonatal Intensive Care Unit (NICU), while the mortality of septic shock was 36 to 40% (Ndugbu, 2020; De Backer et al., 2010). Given the high mortality of septic shock in neonates, it is very important to determine the prognosis in the early stage of the disease. Hemodynamic monitoring is critical for the management of septic shock. Stroke volume (SV), cardiac output (CO), cardiac index (CI) and systemic vascular resistance index (SVRI) are important hemodynamic parameters (De Backer et al., 2010). The purpose of this study was to investigate the value of hemodynamic parameters in estimating the mortality rates of neonates in the early stage of septic shock by analyzing the relationship between hemodynamics and prognosis, which is helpful for the early diagnosis and management, so as to reduce the mortality of these neonates.

MATERIALS AND METHODS

Study design

This is a single center, prospective study conducted from June 2019 to August 2020 in a Level III NICU, which has 30 beds and admits approximately 1200 patients per year. The study was approved by the ethical committees of the

Federal Medical Centre, Umuahia, Nigeria. Informed written consent from the parents of neonates before enrolling them.

All enrolled neonates underwent hemodynamic measurements by the non-invasive cardiac system (NICaS, NI Medical, Israel). The NICaS provided the following hemodynamic parameters: SV, CO, CI, and SVRI. The hemodynamic parameters, which were recorded at the time of diagnosis of septic shock before starting the infusion of saline bolus, were analyzed.

Study population

In this study, neonates were enrolled with evidence of septic shock. Defining sepsis could be challenging, as any definition provided must be context-appropriate so as to properly identify patients. Given the low income environment of this study, the condition for the definition of sepsis is that it be based on clinical syndrome, clinical manifestations and the patient's age. Septic shock is diagnosed if an infant suffered from shock in addition to proven or highly suspected sepsis, and shock was defined by the presence of any of the following criteria: 1) Systolic (SBP) or diastolic blood pressure (DBP) less than fifth percentile for the post-menstrual age. 2) Presence of two or more of the following: capillary refill time > 3 seconds, feeble pulse, core to periphery temperature difference > 3°C, urine output < 0.5 mL/kg/hr, base excess > –5.0 mmol/L, or serum lactate > 5 mmol/L. Sepsis was diagnosed if either or both of the following criteria were met: 1) Blood or/and cerebrospinal fluid culture was positive. 2) Any two of the following sepsis screen variables were positive: C-reactive protein > 10 mg/L, microerythrocyte sedimentation rate > 10 mm after first hour, total leukocyte and absolute neutrophil counts outside the reference range, or immature to total neutrophil ratio > 0.2. Neonates with complex congenital heart disease, congenital organ malformation, and damage defects in the extremities skin were excluded (Schultz et al., 2017; Kissoon and Carapetis, 2015).

Protocol for management in the first hour

Fluid boluses of 10 mL/kg in the first hour, were administered when septic shock happened. After two boluses of fluids, the sign of shock was persistent; inotropes were considered. Dopamine was started at 5 μg/kg/min and up to 10 μg/kg/min. Epinephrine was started at 0.05 μg/kg/min and up to 0.3 μg/kg/min (De Backer et al., 2010). The decision for inotropic support was made by the bedside physicians.

Hemodynamic measurements

Hemodynamic measurements were performed by NICaS, which uses bio-impedance technology, and was demonstrated to be associated with pulmonary artery catheter thermodilution. A previous study demonstrated the agreement between the bio-impedance technology and echocardiography in the neonatal cardiac output measurements (Wu et al., 2020). Each hemodynamic measurement was performed for at least 60 seconds (Wu et al., 2020). Blood pressure was simultaneously measured. SV was measured by applying an alternating electrical resistance, which was calculated by proprietary algorithm. HR was continuously measured by an electrocardiograph (ECG) channel connected to NICaS. CO was calculated as CO = HR×SV. The device calculates cardiac index (CI = CO/body surface area) ml/min/m^2, and systemic vascular resistance index (SVRI = MAP/CI*80) dyn*sec/cm^5*m^2.

Data analysis

All statistical analyses were performed using SPSS-19 software (SPSS, Inc., Chicago, IL, USA). In the descriptive analysis, continuous variables were expressed as mean ± standard deviations (SDs). Comparisons of continuous variables between the two groups were performed using student's t-test. Categorical variables were presented as number and percentage. Comparisons of categorical variables between the two groups were made by the Chi-square test or Fisher's exact test. Predicted probabilities of mortality and 95% CIs were calculated. The receiver operating characteristic (ROC) curve was employed in determining the ideal cut-off values for the hemodynamic parameters for mortality in shock. Cut-off values were evaluated using the max Youden index. The Youden index is calculated as: Youden index = sensitivity + specificity – 1. Based on the cut-off values; sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. $p < 0.05$ was considered statistically significant.

RESULTS

Demographics of the infants with septic shock

A total of 82 neonates with septic shock were enrolled in this study. Table 1 shows the characteristics of the study population. There were 52 survivors and 30 non-survivors. There was no statistical difference in the demographic parameters between the two groups (all $p > 0.05$) (Table 1).

Hemodynamic parameters at the time of diagnosis of septic shock

As shown in Table 2, the hemodynamic parameters of SV, CO and CI were higher in survivors than in non-survivors (all $p < 0.05$). The SVRI was lower at the time of diagnosis of septic shock in survivors than in non-survivors, although without statistical significance ($p = 0.058$) (Table 2).

Table 1. Characteristics of the study population

Parameters	Survivors (n=52)	Non-survivors (n=30)	P-value
Male [n (%)]	37(71.2%)	9	0.789
Gestational age (wk)	37.4±1.3	36.3±3.7	0.065
Birth weight (g)	2855±356	2590±808	0.082
Cesarean section [n (%)]	8(15.4%)	6	0.151
Postnatal age (d)	4.8±3.1	5.2±2.6	0.679
Apgar 1 min	8.6±1.0	7.7±3.0	0.77
Apgar 5 min	9.3±0.6	9.1±1.7	0.525
Apgar 10 min	9.5±0.6	9.6±0.8	0.847
Respiratory support [n (%)]			0.628
None	0	0	
nCPAP	12(23.1%)	4	
MV	40(76.9%)	12	

MV = mechanical ventilation; nCPAP = nasal continuous positive airway pressure.

Table 2. The initial hemodynamic parameters of the infants with septic shock.

Parameters	Survivors (n=52)	Non-survivors (n=30)	P-value
HR (beat/min)	146.6±21.4	149.2±18.9	0.930
SBP	48.6±8.7	46.4±7.8	0.435
DBP	28.1±5.8	27.8±8.3	0.857
MAP	34.6±5.9	33.5±7.5	0.590
SV (ml/kg)	2.30±0.59	1.85±0.55	0.017
CO (ml /min/kg)	337.0±92.5	265.9±59.1	0.014
CI (ml/min/m^2)	4.74±1.09	4.02±1.10	0.044
SVRI [(dyn.s/cm^5）•m^2]	903.9±384.3	1142.5±396.5	0.058

CI = cardiac index; CO = cardiac output; DBP = diastolic blood pressure; HR = heart rate; MAP = mean blood pressure; SV = stroke volume; SVRI = systemic vascular resistance index; SBP = systolic blood pressure.

Table 3. Statistical data of receiver-operating characteristics curve comparisons of different parameters in predicting the outcome value of neonatal septic shock

Parameters	AUC	95%CI	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SV (ml/kg)	0.724	0.566,0.881	1.88	75.0	75.0	40.9	92.9
CO (ml/min/kg)	0.742	0.623,0.861	3.47	91.7	55.7	67.6	96.7
CI (ml/min/m^2)	0.729	0.570,0.888	4.46	91.7	67.3	60.7	97.2

AUC = area under curve; CI = cardiac index, CO = cardiac output, NPV = negative predict value; PPV = positive predict value; SV = stroke volume.

Comparisons of different parameters in predicting the outcome of neonatal septic shock

The ROC curve analyses were used to evaluate the values of SV, CO and CI to predict mortality (Table 3). The AUC values of SV, CO and CI to predict 28-day mortality were 0.724, 0.742, and 0.729, respectively (Table 3). The cut-off values for parameters were 1.88 ml/kg, 345 ml/min/kg, and 4.46 ml/min/m^2 using the max Youden index, respectively. The sensitivity, specificity, PPV, and NPV for the 28-day mortality prediction by each parameter are listed in Table 3.

DISCUSSION

Sepsis is the main reason for the hospitalization of critical neonates. Septic shock is a sepsis stage with high mortality rates (Ndugbu, 2020; De Backer et al., 2010). If the development of the disease is not stopped in the early stage of septic shock, it could rapidly worsen; and lead to death (Nadel et al., 2008).

Therefore, accurately judging the patient's condition and evaluating the severity of the illness is critical to reduce the mortality of septic shock. In this study, the relationship between cardiac output in the early stage of shock and prognosis was analyzed; in order to explore the prognostic value of cardiac output in the early stage of shock. The results showed that SV, CO and CI were decreased in the early stage. ROC curve analysis showed that the value of the three parameters in early prediction of death outcome was close.

Utilizing hemodynamic parameters is the key to the management of septic shock, and cardiac output is an important hemodynamic parameter (De Backer et al., 2010). Shock is a clinical syndrome in which the effective circulating blood volume is reduced and the microcirculation perfusion of important organs is insufficient, leading to the dysfunction of all the organs. Circulatory dysfunction leads to tissue hypoxia and insufficient nutrition supply, which leads to cell dysfunction and eventually cell death (Smith and Herman, 2001).

Septic shock has a greater impact on microcirculatory perfusion of important organs than other types of shock (De Backer et al., 2010). The noninvasive hemodynamic monitoring system used to monitor the hemodynamics of neonates with shock. The results showed that during septic shock, the neonates had the characteristics of high discharge and low resistance, such as the increase of SV, CO and CI, and the decrease of systemic resistance. However, the early symptoms of neonatal septic shock are often atypical and lack specificity, so they can be easily ignored, until the occurrence of hypotension, which is often life-threatening. In order to prevent irreversible pathological changes, it is necessary to improve the peripheral circulation, increase cardiac output and restore cell function at the earliest (De Backer et al., 2010).

Neonatal septic shock can cause myocardial inhibition and vascular smooth muscle dysfunction (Chen and Shi, 2019). About 50% of septic shock patients have different degrees of myocardial injury. Clinical studies have found that myocardial injury is one of the important pathological characteristics of death in septic shock patients (Fleischmann-Struzek et al., 2018). A meta-analysis of six studies showed that the decrease of left ventricular systolic function is related to the mortality of septic shock. A previous study showed that the decrease of cardiac output in the early stage of sepsis is related to the clinical outcome (Perny et al., 2014).

Through ROC curve analysis, AUC of SV, CO and CI were compared and it was found that AUC of the three parameters had insignificant difference. The sensitivity, specificity, PPV, and NPV of each hemodynamic parameter were compared. CO achieved the highest AUC, sensitivity and PPV in predicting mortality.

When neonates with septic shock are given rapid fluid resuscitation in the early stage, it may lead to or worsen multiple complications, such as systemic tissue edema, heart failure, respiratory failure or brain edema, and even increase the mortality, especially if their hemodynamic abnormality cannot be accurately judged and the excessive fluid treatment is continued (Chen et al., 2015; Weiss et al., 2015). In septic shock patients, fluid resuscitation and the reduction of fluid balance under the guidance of SV is associated with clinical outcomes (Sankar et al., 2017). SV monitoring in fluid resuscitation can reduce the fluid load, shorten the time of mechanical ventilation, shorten the time of using vasoactive drugs, and reduce the probability of hemodialysis (Smith and Herman, 2001).

Conclusion

Using such important parameters as SV, CO and CI could be valuable as guides in the management of septic shock patients, so as to improve the prognosis. This reaffirms hemodynamic monitoring as an essential model for the diagnosis and therapeutic management of critically ill patients, especially neonates.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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